Exhibit B
09/720,086

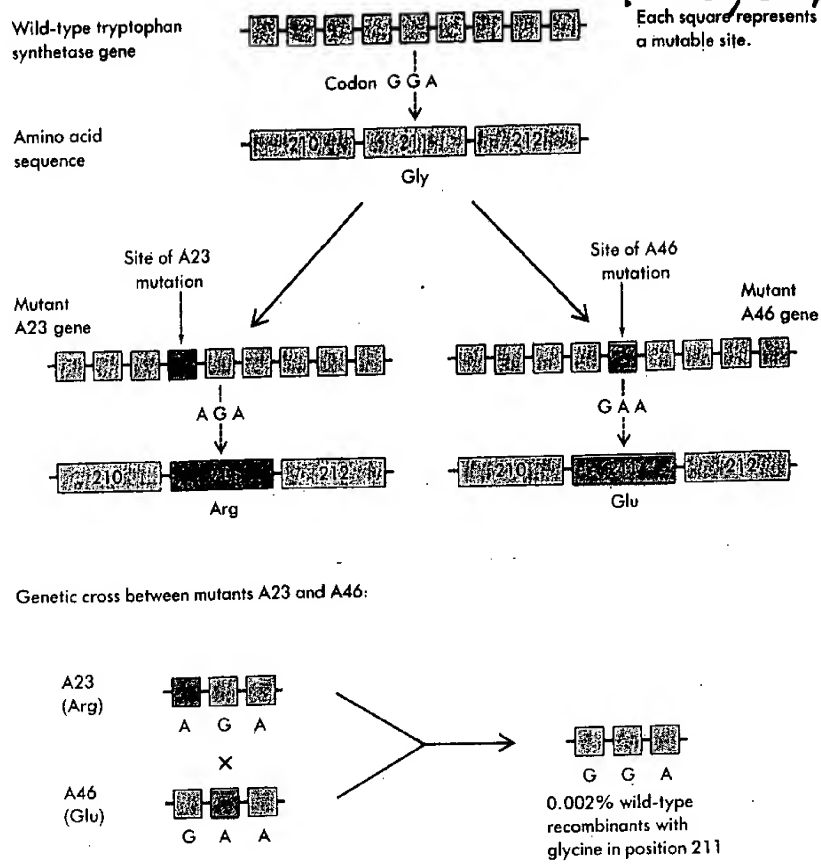

Figure 8-14
Demonstration that a single amino acid is specified by more than one mutable site. We now know that the mutable sites are DNA bases and the codons are actually bases complementary to these in mRNA. (After Emanual J. Murgola.)

in which the amino acid in position 212 is replaced by another amino acid. Most significantly, the type of replacement differs for strains A23 and A46. Besides back-mutating to glycine, strain A23 mutates to threonine and serine, whereas A46 mutates to alanine and valine in addition to glycine. The failure of A23 ever to give rise to alanine or valine and the failure of A46 ever to mutate to threonine or serine is very difficult to explain if their differences from wild type are based on alternative configurations of the same mutable site. But these mutational patterns make perfect sense if glycine at the 212 position is coded by GGA with the A23 mutation to arginine representing a G to A change at the first position of the codon to give rise to AGA and the A46 mutation to glutamic acid occurring at the middle (second) position to give rise to GAA. Their divergent subsequent mutations to serine and threonine and to alanine and valine, respectively, can also be understood by inspecting the genetic code (Figure 8-15).

Single Amino Acid Substitutions Usually Do Not Alter Enzyme Activity

The ability of a polypeptide chain to be enzymatically active does not require an exactly specified amino acid sequence. This is shown by examination of the new mutant strains obtained by treating strains A23 and A46 with mutagens. The possession of either glycine or serine in position 212 yields a fully active enzyme, whereas threonine in

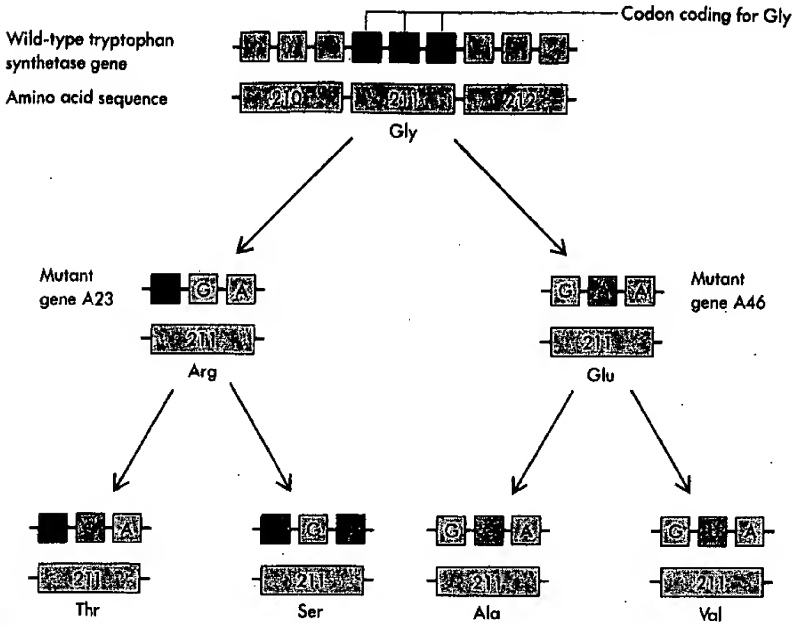

Figure 8-15
Formation of mutants A23 and A46 and their subsequent mutations. Notice that Thr and Ser cannot result from a single base change to the codon for Glu; likewise, Ala and Val cannot result from only one base change to the codon for Arg. Therefore, the A23 and A46 mutants must occur from mutations at two different mutable sites, as shown in Figure 8-14.

the same position yields an enzyme with reduced activity, demonstrating that the activity of an enzyme does not demand a perfectly unique amino acid sequence (Figure 8-16). In fact, evidence now indicates that amino acid replacements in many parts of a polypeptide chain can occur without seriously modifying catalytic activity. However, one sequence may often be best suited to a cell's particular needs, and it is this sequence that is encoded by the wild-type allele. Even though other sequences are almost as good, they will tend to be selected against in evolution.

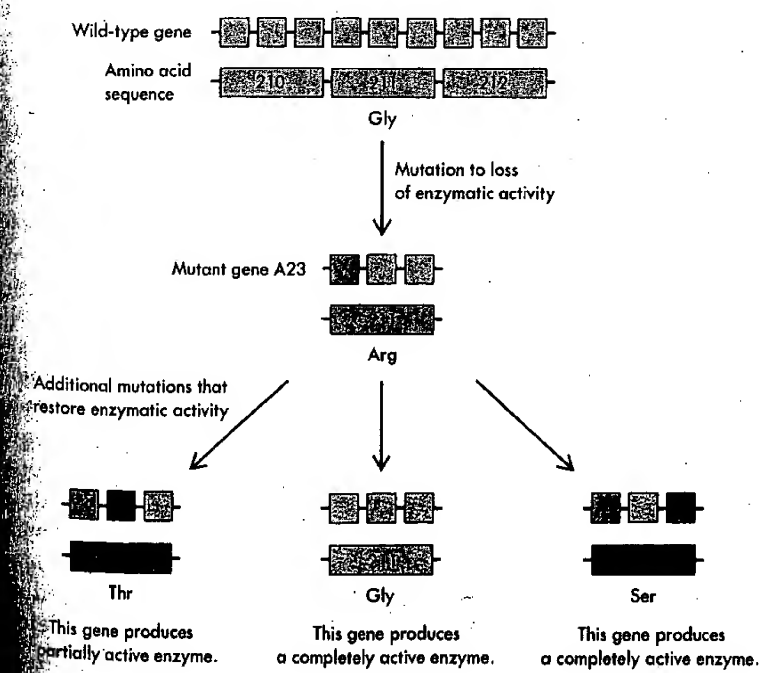

Figure 8-16
Evidence that many amino acid replacements do not result in loss of enzymatic activity.

VOLUME I GENERAL PRINCIPLES

MOLECULAR BIOLOGY OF THE GENE

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